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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,568	10/23/2003	Hirohiko Tsuzuki	Q77913	5986
23373	7590	01/12/2006	EXAMINER	
SUGHRUE MION, PLLC 2100 PENNSYLVANIA AVENUE, N.W. SUITE 800 WASHINGTON, DC 20037			SINGH, SATYENDRA K	
			ART UNIT	PAPER NUMBER
			1651	

DATE MAILED: 01/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/690,568	Applicant(s) TSUZUKI ET AL.	
	Examiner Satyendra K. Singh	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 14 November 2005.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-6,8-10,14 and 15 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4,8-10 and 14 is/are rejected.
- 7) ☒ Claim(s) 5, 6 and 15 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

Applicant's response (and the amendment to claims) to the office action filed on November 14<sup>th</sup> 2005 is duly acknowledged.

Claims 1-6, 8-10 and 14-15 are pending in the application, and are examined on their merits, hereafter.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

**Claims 1-4, 8-10 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hara et al (U.S. Patent 6,821,107 B1, [A]) in view of Esser et al [U].**

Claim 1 is drawn to a method for detaching a carrier for cell culture from a cultured cell formed on a surface of said carrier for cell culture, which comprises the step of bringing the carrier for cell culture into contact with a compound represented by

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the following **formula (I)** or a polyphosphoric acid or a salt thereof: (as claimed in the instant specification-see page 24) wherein L11 represents a substituted or unsubstituted divalent hydrocarbon group; and M represents hydrogen atom or a cation.

Claim 2-4 (see specific recitations in the instant claims 2-4) drawn to variations of the method of claim 1- Claim 2 is drawn to a method for culturing a cell; claim 3 is drawn to a method for transferring a cell; and claim 4 is drawn to a method for laminating cell layers.

Claims 8-10 however, are drawn to methods of detaching a carrier for cell culture using **a compound represented by the formula (I), or (II), or (III)** with various substitutions at L and R groups as claimed, which are exemplified by compounds, namely 1-hydroxyethane-1,1-diphosphoric acid (HEDP/EHBP) and ethylenediamine-N,N,N',N'-tetrakis(methylenephosphoric acid) (EDTPO/EDTMP) used in the instant invention (see instant specification, page 20-22, in particular).

Claim 14 (new) is drawn to the method according to claim 1, wherein the carrier for cell culture is brought into contact with the compound represented by formula (I) for a period of from 5 minutes to 2 hours to effect a removal treatment.

Hara et al [A] teach a method of forming a structure having multiple cell layers using carrier for cell culture made of calcium alginate and collagen gel layers on a porous membrane support. Hara et al [A] also teaches laminated carriers for cell culture, method for culturing cells using the carriers, method of transferring cultured cells obtained by the method of culturing cells and detaching them from the carrier for cell culture using a chelating compound such as EDTA, a method of laminating (piling up) another cell layer on the cultured cell layer, and a cell multi-layer obtained by this lamination procedure (see Hara et al [A], entire document).

However, the step of bringing the carrier for cell culture into contact with a compound represented by formula (I), formula (II), or formula (III) for the methods such as claimed, is not explicitly disclosed by Hara et al [A].

Esser et al [U], using copper-complexation index, teach the fact that chelating agents include (among others such as EDTA, EGTA, etc.) compounds, namely 1-hydroxyethane-1,1-diphosphoric acid (HEDP/EHBP) and ethylenediamine-N,N,N',N'-tetrakis(methylenephosphoric acid) (EDTPO/EDTMP) that are also exemplified by the instant invention (see instant specification, page 20-22, in particular), and are known to be used as chelating agents in the prior arts (see Esser et al [U], abstract, introduction, results & discussion, pages 250, 251 and 255, in particular).

Since the structural limitations of claims 1-10 using a compound for detaching the cell culture carrier from cultured cell formed on a surface as represented by formulas (I), (II) and (III) are met by the species of compounds such as HEDP and EDTPO/EDTMP that are exemplified by the instant specification (see pages 20-22, in particular), it would have been obvious to a person of ordinary skill in the art at the time this invention was made to modify the method for detaching a carrier for cell culture from a cultured cell formed on a surface of said carrier for cell culture comprising the step of bringing the cells culture carrier into contact with a compound as taught by Hara et al [A] such that a compound used for the method for detaching the carrier such as claimed is represented by the formula (I), (II), and (III) such as HEDP or EDTPO/EDTMP as taught by Esser et al [U].

The person of ordinary skill in the art would have been motivated to modify the method by substituting the chelating agent EDTA used in the referenced method of Hara et al [A] with safer, effective, and biocompatible chelating agents such as organophosphates, HEDP, EDTPO/EDTMP, and/or their derivatives as taught by Esser

et al [U] because of their functional equivalence in terms of their chelating properties recognized by art at the time this invention was made.

One of ordinary skill in the art would have had a reasonable expectation of success when updating the method for detaching the carrier for cell culture as taught by Hara et al [A] by the above mentioned organophosphates or polyphosphoric acid or salts thereof such as taught by Esser et al [U], because the chelating properties of such compounds is clearly demonstrated by Esser et al [U].

*In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. In re Ruff, 256 F.2d 590, 118 USPQ 340 (CCPA 1958).*

*An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)- see MPEP 2144-06).*

The limitations of claim 14 (i.e. time period, 5 minutes to 2 hours to effect a removal treatment) clearly would have been a routine matter of optimization on the part of an artisan of ordinary skill, the said artisan recognizing that it is a routine procedure to optimize the time periods associated with the process of detaching a carrier from the cell culture (as well as attendant process steps as evidenced by the fact that Hara et al teach the durations for the steps involved in cell culture at optimal temperature, optimal gelation time for calcium alginate layer, optimal concentrations of the ingredients used, and incubation conditions and periods; see Hara et al, Figures 1-3 and examples 1-3, in particular). Furthermore, given the fact that Hara et al teach the removal of the calcium alginate layer (using EDTA solution, 0.05 to 0.2 M, allowed to soak through the porous membrane of extracellular matrix material), it would have been a matter of routine

optimization of the time period to effect the removal treatment as well as of the method for detaching a carrier for cell culture as claimed in the instant invention. A holding of obviousness over the cited claims is therefore clearly required.

As per MPEP 2144.05 [R3], II. OPTIMIZATION OF RANGES - A. Optimization Within Prior Art Conditions or Through Routine Experimentation: *Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."* *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235

Thus the entire invention as a whole would have been *prima facie* obvious to one skilled in the art at the time the claimed invention was made.

#### ***Response to applicant's arguments***

The rejection of claims **1-4, 8-10 and 14** (newly amended) under 35 USC § 103(a) over Hara et al [A] in view of Esser et al [U] is maintained.

Applicant's arguments (see applicant's remarks, page 10-11, in particular) are interesting and persuasive. However, the claimed method (as amended) does not bring the limitations of claims 5, 6, and 15 into the broader claim 1, and therefore, the method as claimed is still deemed obvious over Hara et al [A] in view of Esser et al [U] as discussed above. Applicant's argument that "*a prima facie case of obviousness has not and cannot be established based on Hara et al and Esser et al, as Esser does not teach the solubilization of alginic acid gels with the chelating agents disclosed therein, and appears to only teach the copper chelating property of theses agents; and there is no reason why a person of ordinary skill in the art would have been motivated to perform the method of Hara with other chelating agents taught by Esser, with a reasonable*

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*expectation of success*" (see page 11 of applicant's remarks), is not found persuasive because Hara et al (and not Esser et al) do teach solubilization of alginic acid gels with the chelating agent such as EDTA, and in view of the disclosure provided by Esser for the functional equivalency of the compounds (HEDP, EDTMP, as claimed in the instant invention) as chelating agents (albeit for another divalent cation such as copper), it would have been obvious to a person of ordinary skill in the art to modify the procedure of Hara et al with a reasonable expectation of success. In fact, Hara et al disclose the fact that "the chelating agent can be selected appropriately according to the type of a multivalent metal ion (including copper; see Hara et al, column 3, lines 38-52; that can be used for gelation of alginic acid) which forms a chelate structure with a carboxylic acid group in the molecule of alginic acid" (see Hara et al, column 6, lines 36-39, and claim 16, in particular) such as citric acid, for example.

Applicant's arguments have been fully considered and were not found persuasive. Accordingly, the rejection of the record is maintained.

***Allowable subject matter***

Claims 5, 6 and 15 are objected to as being dependent upon a rejected base claim, but contain allowable subject matter if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Conclusion***

**No claims are allowed.**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).




A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyendra K. Singh whose telephone number is 571-272-8790. The examiner can normally be reached on 9-5MF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
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Art Unit 1651



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